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THE POISON PEN

Will There Ever be an Antidote for Drug Shortages?

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Clinicians familiar with news stories highlighting common drug shortages such as saline solution and anti-hypertensives may be surprised that this persistent public health crisis extends to many common antidotes [1]. Unlike other drug shortages where some product may still be available (albeit a less preferred strength or formulation), antidotes are at a higher risk of significant shortages where no product at all is available. Many antidotes typically do not have a large market share and are generally manufactured by a single company in a single presentation [1]. One such antidote has faced a critical shortage since May 2020 [2]. British Anti-Lewisite (BAL, dimercaprol) is a well-known antidote for the treatment of lead encephalopathy and toxicity from other metals, and it is considered an essential medication by the World Health Organization [3]. According to the American Society of Health-System Pharmacists, BAL has been impacted by 4 discrete shortages since 2006, including the current shortage due to manufacturing problems and regulatory delays [2].

The shortage of BAL has significant implications for patients, particularly those with lead encephalopathy, a life-threatening condition that requires prompt treatment. Administration of calcium disodium EDTA alone can increase the distribution of lead into the central nervous system and is not recommended. Two alternatives to BAL are succimer and unithiol; however, there are limited data supporting their efficacy in the setting of encephalopathy [4]. Additionally, there are logistic considerations when using these alternatives, including the ability to use the oral route in encephalopathy, and for unithiol, the need to have it prepared by a compounding pharmacy, which often has a turnaround time of at least 24 hours. This may lead to suboptimal therapy and unacceptable delays in treatment for critically ill patients.

Like many other drug shortages, the shortage of BAL is a result of a lack of resiliency in the supply chain. One point of failure with a single company providing a life-saving product places patients at risk if there is not a plan for redundancy in the system. In the past, the Food and Drug Administration (FDA) has been able to extend the expiration date of available product if the manufacturer can provide stability data; however, in the case of BAL, the manufacturer has no additional details to provide [5]. As such, short-term mitigation strategies are limited. In order to ensure appropriate treatment of poisoned patients, institutions must vigilantly monitor supply and proactively develop protocols to use alternative chelators with the best available, although limited evidence. Outcomes data should be collected when alternative chelators are used to inform treatment protocols. Clinicians should also report cases when BAL is unavailable for a patient to the FDA via MedWatch or on the FDA drug shortage website.

Solutions to the drug shortage problem have been proposed, but few have been enacted. FDA's Drug Shortage Task Force recommends developing a quality rating system to incentivize drug manufacturers to invest in quality facilities as well as promote sustainable contracts to ensure a reliable supply [6]. The CARES Act states that manufacturers must develop risk management and redundancy plans for their supply chains, but this will take time and required actions and accountability are not well defined [7]. Ongoing work by the National Academies of Sciences, Engineering, and Medicine to evaluate the security of the medical product supply chain may also provide solutions [8]. Engagement of industry and balanced incentives are additional potential strategies. While these interventions are taking place in the USA, it is also important to consider that the burden of lead and other heavy

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metal toxicity is greater in developing countries where access to antidote is even more limited. Ultimately, a multifaceted approach will be required to ensure that life-saving antidotes such as BAL continue to be available for patients in both the USA and worldwide.

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